PCT

Form PTO-1390 (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
2296.2320	
U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	
09/806915	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/GB99/03288	06 October 1999 (06.10.99)
PRIORITY DATE CLAIMED	
06 October 1998 (06.10.98) and 15 October 1998 (15.10.98)	

TITLE OF INVENTION

ANIMAL STEREOTYPY

APPLICANT(S) FOR DO/EO/US

Christine NICOL and Patricia HARRIS

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 into English (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 into English (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: International Preliminary Examination Report; International Search Report

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/806915	PCT/GB99/03288	2296.2320

21. ☐ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5):		
Search Report has been prepared by the EP or JPO **$860.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$690.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(1)) but international search fee paid to USPTO (37 CFR 1.492(a)(2)) **$710.00**		
Neither international preliminary examination fee (37 CFR 1.492(a)(1)) nor international search fee (37 CFR 1.492(a)(2)) paid to USPTO **$1,000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(4)) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed		Number Extra	Rate		
Total Claims	62	-20 =	42	X **$18.00**	$ 756.00	
Independent Claims	4	- 3 =	1	X **$80.00**	$ 80.00	
Multiple dependent claim(s) (if applicable)				+ **$270.00**	$ 270.00	
				TOTAL OF ABOVE CALCULATIONS =	$ 2,106.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				+	$	
				SUBTOTAL =	$ 2,106.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)).					$	
				TOTAL NATIONAL FEE =	$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$	
				TOTAL FEES ENCLOSED =	$ 2,106.00	
				Amount to be:		
				refunded	$	
				charged	$	

a. ☒ A check in the amount of $ 2,106.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1205 . A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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34,382
REGISTRATION NUMBER

2296.2320 PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Christine NICOL et al.	:	Examiner: Not yet assigned
Application No.: 35 U.S.C. 371 of PCT/GB99/03288 filed October 6, 1999	:	Group Art Unit: Not yet assigned
Filed: Herewith	:	Date: April 5, 2001
For: ANIMAL STEREOTYPY		

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 26, 27 and 31-33 without prejudice.

Kindly amend claims 3-6, 8-10, 16-19, 21-23, 25 and 28-30 as follows. A marked-up copy of the amended claims, showing the changes made thereto, is attached.

3. (Amended) A composition according to claim 1 or 2 in which the amount of fat in the composition is from about 5% to about 20%, by weight of the composition.

4. (Amended) A composition according to claim 1 or 2 in which the amount of crude fibre in the composition is from about 3.5% to about 35%, by weight of the composition.

5. (Amended) A composition according to claim 1 or 2 in which the amount of neutral detergent fibre in the composition is from about 15% to about 70%, by weight of the composition.

6. (Amended) A composition according to claim 1 or 2 in which at least some of the fibre is chopped fibre.

8. (Amended) A composition according to claim 1 or 2 in which the starch content of the composition is below about 20% by weight of the composition.

9. (Amended) A composition according to claim 1 or 2 in which the antacid inhibits secretion of acid in the stomach.

10. (Amended) A composition according to claim 9 in which the antacid is a proton pump inhibitor or a histamine type-2 antagonist.

16. (Amended) A method according to claims 11, 12 or 13, in which the stomach pH of the animal is controlled from birth.

17. (Amended) A method according to claims 11, 12 or 13, in which the stomach pH of the animal is controlled by inhibiting secretion of acid in the stomach of the animal.

18. (Amended) A method according to claim 17 in which the acid secretion is inhibited by administering a proton pump inhibitor or a histamine type-2 antagonist to the animal.

19. (Amended) A method according to claims 11, 12 or 13, in which the stomach pH of the animal is controlled by administering a composition comprising fat, fibre and optionally a stomach antacid to the animal.

21. (Amended) A method according to claim 19 in which the composition is included in the diet of the animal's mother when she is lactating.

22. (Amended) A method according to claim 19, in which the composition is included in feed and said feed is fed to the animal as it is being weaned.

23. (Amended) A method according to claims 11, 12 or 13, in which the stomach pH of the animal is controlled shortly before and/or during and/or following weaning, ingestion of a high grain diet, or a period of extended fasting by the animal.

25. (Amended) A method according to claim 24 in which ulcer formation is prevented or reduced, or ulcers are treated, by administering a composition comprising fat, fibre and optionally a stomach antacid to the animal.

28. (Amended) A method according to claims 11, 12 or 13, in which the animal is an *equidae*, a non-ruminant omnivore, or a non-ruminant herbivore.

29. (Amended) A method according to claim 28 in which the animal is a horse.

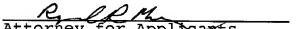
30. (Amended) A method according to claim 29 in which the stereotypy is crib-biting.

REMARKS

Claims 1-25 and 28-30 are presented for examination. Claims 3-6, 8-10, 16-19, 21-23, 25 and 28-30 have been amended to remove improper multiple dependencies and correct other informalities. Claims 26, 27 and 31-33 have been cancelled without prejudice. Favorable consideration of the present claims is respectfully requested.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES
MADE TO THE CLAIMS

3. (Amended) A composition according to claim 1 or 2 in which the amount of fat in the composition is from about 5% to about 20%, [preferably from about 8% to about 17%,] by weight of the composition.

4. (Amended) A composition according to [any preceding] claim 1 or 2 in which the amount of crude fibre in the composition is from about 3.5% to about 35%, [preferably from about 10% to about 25%,] by weight of the composition.

5. (Amended) A composition according to [any preceding] claim 1 or 2 in which the amount of neutral detergent fibre in the composition is from about 15% to about 70%, [preferably from about 25% to about 50%,] by weight of the composition.

6. (Amended) A composition according to [any preceding] claim 1 or 2 in which at least some of the fibre is chopped fibre.

8. (Amended) A composition according to [any preceding] claim 1 or 2 in which the starch content of the composition is [low, preferably] below about 20% by weight of the composition.

9. (Amended) A composition according to [any preceding] claim 1 or 2 in which the antacid inhibits secretion of acid in the stomach.

10. (Amended) A composition according to claim 9 in which the antacid is a proton pump inhibitor [such as omeprazole,] or a histamine type-2 antagonist.

16. (Amended) A method according to [any of claims 11 to 14] claims 11, 12 or 13 in which the stomach pH of the animal is controlled from birth.

17. (Amended) A method according to [any of claims 11 to 16] claims 11, 12 or 13 in which the stomach pH of the animal is controlled by inhibiting secretion of acid in the stomach of the animal.

18. (Amended) A method according to claim 17 in which the acid secretion is inhibited by administering a proton pump inhibitor[, such as omeprazole,] or a histamine type-2 antagonist to the animal.

19. (Amended) A method according to [any of claims 11 to 18] claims 11, 12 or 13 in which the stomach pH of the animal is controlled by administering a composition [according to any of claims 1 to 10] comprising fat, fibre and optionally a stomach antacid to the animal.

21. (Amended) A method according to claim 19 [or 20] in which the composition is included in the diet of the animal's mother when she is lactating.

22. (Amended) A method according to [any of claims 19 to 21] claim 19 in which the composition is included in feed and [the] said feed is fed to the animal as it is being weaned.

23. (Amended) A method according to [any of claims 11 to 22] claims 11, 12 or 13 in which the stomach pH of the animal is controlled shortly before and/or during and/or following weaning, ingestion of a high grain diet, or a period of extended fasting by the animal.

25. (Amended) A method according to claim 24 in which ulcer formation is prevented or reduced, or ulcers are treated, by administering a composition [according to any of claims 1 to 10] comprising fat, fibre and optionally a stomach antacid to the animal.

28. (Amended) A method according to [any of claims 11 to 25 or use according to claim 26 or 27] claims 11, 12 or 13 in which the animal is an *equidae*, a non-ruminant omnivore, or a non-ruminant herbivore.

29. (Amended) A method [or use] according to claim 28 in which the animal is a horse.

30. (Amended) A method [or use] according to claim 29 in which the stereotypy is crib-biting.

Animal Stereotypy

The present invention relates to the treatment, prevention or amelioration of animal stereotypies.

Stereotypies are animal behavioural disorders. They are characterised by the performance of repetitive, invariant movements which have no obvious function. Equine stereotypies are of particular concern to owners of horses because the condition and performance of a horse which displays stereotypic behaviour is often adversely affected. This can substantially reduce the market value of a horse. Equine stereotypies include oral stereotypies such as crib-biting, wood chewing and wind-sucking, and locomotor stereotypies such as weaving and box-walking.

The cause or causes of stereotypies are not known. This lack of knowledge has severely hampered the development of effective treatments and preventatives for stereotypies. In the abstract of a study by Christine Nicol and Amanda Waters, entitled "The treatment and Prevention of Equine Stereotypies", theories on possible causes of equine stereotypy are given. It is noted that stereotypies are frequently regarded as functionless pathologies of the nervous system. It has also been proposed that oral stereotypies serve some digestive function. Alternative views are that they are developed by an animal as a way of dealing with stress or boredom. A further theory is that animals learn to perform stereotypies by imitating other animals that perform them.

Preventative measures for equine stereotypy based on these theories include use of stable toys to stop a horse from becoming bored or stressed, or isolation of a horse from other horses to stop it from learning stereotypies by imitation. Treatment of oral stereotypies such as crib-biting can involve more harsh measures, for example fitting

the horse with a collar to prevent it from crib-biting, or even surgery. Typically, surgery involves cutting the ventral neck muscles and/or the nerves that supply them. Other forms of control include aversion therapy. Here, the horse may be given an electric shock, or physical admonishment when it performs a stereotypy.

The above treatments or preventative measures have been found to be unsatisfactory. Use of stable toys has not been found to be an effective way of preventing equine stereotypy. Physical prevention of stereotypy, either by use of a collar or surgery, is not successful because the animal still has the urge to perform the behaviour. When the collar is removed, a horse will often perform a stereotypy more intensively than before. After surgery, the animal may still be able to perform the stereotypy by utilising other muscle groups. Preventatives such as social isolation, collar fitting, aversion therapy and surgery are undesirable.

In the abstract by Nicol and Waters referred to above, it is disclosed that an epidemiological study has shown that a significant number of horses develop stereotypic behaviour during the immediate post-weaning period. At weaning, the mare-foal bond is broken, but feeding and housing practices are often also changed at this time. The discovery that stereotypic behaviour often begins in the immediate post-weaning period has not so far led to a treatment or preventative for stereotypy because it is not clear which factor or combination of factors are significant in the onset of stereotypy.

Some studies have reported a link between behavioural abnormalities and acidity in the hindgut. Johnson *et al* (Equine Veterinary Journal 1998, 30(2), 139-43) noted a reduction in abnormal behaviour when horses were administered Founderguard (containing 1% virginiamycin). The most obvious explanation for this is stated to be reduced

acidosis in the hindgut caused by suppression by virginiamycin of lactic acid production in the hindgut.

Willard *et al* (Journal of Animal Science 1977, 54(1), 87-92) discloses that horses fed a concentrate diet with hourly infusions of sodium carbonate were observed to spend less time chewing wood and performing coprophagy (eating faeces) than horses fed a concentrate diet alone. The infusions of sodium carbonate significantly increased caecal pH. It was concluded that increased caecal acidity may influence the horse's desire to practice coprophagy and wood chewing.

The link between acidity in the hind gut and abnormal behaviour is also reported in WO 96/20709. This document discloses that starch, sugar or other carbohydrate which enters the hind gut is rapidly fermented to form lactic acid. This accumulation of lactic acid is stated to lead to a decline in hindgut pH which results in a wide range of biological consequences, including behavioural abnormalities. Methods of treatment or prophylaxis of adverse behaviour are disclosed in which an effective amount of an agent capable of preventing or controlling fermentative acidosis in the hindgut is administered to an animal.

Agents disclosed in WO 96/20709 as being capable of preventing or controlling fermentative acidosis are: antibiotic type compounds such as Virginiamycin (stated to be active against bacteria which produce lactic acid); enzymes which increase the digestion of carbohydrate and decrease the amount of rapidly fermentable carbohydrate passed to the hindgut; and clay preparations which bind specific ions to reduce the adverse effects of rapid fermentation of starch and other soluble carbohydrates in the gastrointestinal tract.

However, there are disadvantages to use of these agents. Virginiamycin is believed to have growth promoting activity. Consequently, this side effect may make

administration of Virginiamycin undesirable. The efficacy of enzymes which increase the digestion of carbohydrate is thought to be low because the rate of passage of enzymes through the gut can be rapid and their activity may be reduced by the low pH at certain points in the gut. It is likely that high levels of clay preparation are required to be effective in reducing hind gut pH. It may be undesirable to feed an animal the levels of clay that are required to have an effect.

It is also believed that hindgut acidity is not the principal cause of at least some stereotypies. Consequently, treatments which reduce hindgut acidity may not be wholly effective and may not have any effect at all on some stereotypies.

There is, therefore, still an urgent need to provide effective treatments, preventatives or amelioratives for stereotypy which do not involve any undesirable practices being performed on an animal being treated.

We have now appreciated that there is a link between low stomach pH and behavioural abnormality. This link has not previously been recognised and has provided new compositions and methods for the treatment, prevention or amelioration of animal stereotypy.

According to the invention there is provided a composition for use in the treatment, prevention or amelioration of animal stereotypy which comprises fat, fibre, and optionally a stomach antacid.

According to the invention there is also provided a pharmaceutical composition for use in the treatment, prevention or amelioration of animal stereotypy which comprises fat, fibre, and optionally a stomach antacid, together with a pharmaceutically acceptable carrier, excipient or diluent.

There is further provided according to the invention use of a composition according to the invention in the

manufacture of a medicament for the treatment, prevention, or amelioration of animal stereotypy.

There is also provided according to the invention use of a stomach antacid in the manufacture of a medicament for the treatment, prevention, or amelioration of animal stereotypy.

There is also provided according to the invention a method of treatment, prevention, or amelioration of animal stereotypy which comprises controlling the stomach pH of an animal.

The stomach pH of the animal may be controlled by administering a composition according to the invention to the animal.

There is also provided according to the invention a method of treatment, prevention, or amelioration of animal stereotypy which comprises preventing or reducing ulcer formation in the stomach of an animal or treating ulcers formed in the stomach of an animal. Ulcer formation may be prevented or reduced, and ulcers may be treated, by administering a composition according to the invention to the animal.

The amount of fat in compositions according to the invention is preferably from about 5% to about 20%, more preferably from about 8% to about 17%, by weight of the composition. Preferred fats are highly polyunsaturated vegetable oils. These fats tend to be highly palatable and easily mixed into other components of compositions of the invention. Examples are corn oil, soya oil, or processed canola oil. Other preferred fats are more saturated fats which are more stable and, therefore, are less prone to rancidity. Examples are coconut oil, palm oil, or sunflower oil.

"Fibre" as used herein means carbohydrate which is not digestible by mammalial enzymes. Some of the fibre may be fermentable by microbial enzymes. The amount of fibre in compositions according to the invention should be sufficient

to extend the amount of time spent chewing the composition by an animal administered with such a composition. The amount of fibre in a composition of the invention may be measured as the amount of crude fibre or neutral detergent fibre (NDF). The amount of crude fibre in compositions according to the invention is preferably from about 3.5% to about 35%, more preferably from about 10% to about 25%, by weight of the composition. The percentage of crude fibre in a sample is the percentage of the matter remaining in the sample after treatment with acid and alkali. This is measured by treating the defatted sample successively with boiling solutions of sulphuric acid and sodium hydroxide. The residue is filtered, washed, weighed and ashed. The loss of weight on ashing corresponds to the weight of fibre present in the test sample. The amount of NDF in compositions according to the invention is preferably from about 15% to about 70%, more preferably from about 25% to about 50%, by weight of the composition. This can be calculated using a method such as that described in Agric. Handbook No.379 (1970) Goering H.H. and Van Soest P.T. (USDA Washington D.C.).

Preferably at least some of the fibre is chopped fibre. Preferably the chopped fibre is about 1-7cm long. Preferably at least some of the fibre also has a high protein concentration. A preferred example is alfalfa hay.

The starch content of compositions according to the invention is preferably low, suitably below about 20% by weight of the composition. Feed stuffs which comprise high amounts of fat and fibre and low amounts of starch are especially preferred as components of compositions of the invention. An example is rice bran.

Suitable stomach antacids for use in compositions and methods of the invention may act by neutralising stomach acid or by inhibiting secretion of acid into the stomach. Any alkali which neutralises stomach acid and can be safely administered to an animal may be used. Suitable antacids

which act by neutralising stomach acid include Neigh-Lox and prostaglandin analogues. The active ingredients in Neigh-Lox are dihydro-aluminium sodium carbonate and aluminium phosphate. Suitable antacids which inhibit acid secretion in the stomach include proton pump inhibitors and histamine type-2 antagonists which block histamine-stimulated gastric acid secretion. Substituted benzimidazoles, such as omeprazole, act as proton pump inhibitors. Cimetidine and ranitidine are examples of Histamine type-2 antagonists.

It is believed that once an animal has learnt a stereotypy, the stereotypic behaviour becomes fixed and the animal will perform the stereotypy even if the original cause of the behaviour has been removed. Consequently, the animal should be treated using a composition or method according to the invention before any stereoptypic behaviour becomes fixed, and preferably before, or soon after, the animal develops any stereotypic behaviour.

Acidity in the stomach is thought to increase when animals are fed meals of grain or are subjected to extended periods of fasting. Stomach pH may also decrease when the diet of an animal changes during weaning. Consequently, an animal should be treated with a composition or method according to the invention shortly before and/or during and/or following eating a high grain diet, undergoing a period of extended fasting, or weaning. Treatment at these times may be particularly effective in preventing, treating, or ameliorating animal stereotypy.

In order to minimise the risk of an animal developing a stereotypy, the animal may be treated with a composition or method according to the invention from birth.

Compositions and methods of the invention may also be effective when the animal being treated is a weaned animal.

It is considered that compositions according to the invention will usually be included with the diet of an animal being treated according to the invention.

Compositions according to the invention may be included in the diet of the animal's mother while she is lactating. This is because the mother's diet influences the nutritional content of the milk which the animal receives and because the animal may eat its mother's feed before it is weaned; foals invariably eat their dam's feed before they are weaned.

Compositions according to the invention may be included in feed and the said feed fed to the animal as it is being weaned onto solid food.

Compositions according to the invention may be included in the animal's diet post weaning.

The invention is further described by the following embodiment. The embodiment relates to use of stomach antacid to treat, ameliorate, or prevent crib biting in horses.

Example

Methods

Advertisements were placed for foals to take part in the study. Foals offered for the study were rejected if the foal had been crib-biting for more than 20 weeks, was more than 1 year of age, or if the owner had attempted to prevent crib-biting using surgery or electric shock treatments.

Foals chosen for the study were visited at times when the owners had previously noted crib-biting behaviour. They were observed for a minimum of 1 hour to establish that they were performing crib-biting behaviour. It was clear from the observations that some owners had mistaken wood-chewing for crib-biting.

A crib-biting horse grasps a fixed object with its incisor teeth, arches its neck, and pulls back (often but not always

emitting a grunting sound). There is no ingestion of wood, or other substrate. The behaviour is invariant in form - it tends to occur in the same place, or perhaps 2 or 3 favoured sites, within the stable, at the same time in a sequence of behaviour (for example a horse may grasp a piece of hay, move to the front of its stable, then crib-bite), and at the same times of day (for example just after feeding). The crucial part of crib-biting is arching of the neck which puts considerable tension on the neck muscles, and affects the oesophagus and pharynx.

Wood chewing is completely different and cannot be distinguished in form from normal chewing at hay, straw or bark. Wood or other material is ingested and chewed. The wood or material may or may not be swallowed. The horse is not tense during this behaviour. A horse will perform wood-chewing in a variety of places (wherever a new bit of wood can be found), and does not perform the behaviour as part of a fixed sequence of behaviour.

Those foals observed to be wood-chewing were rejected from further study. The remaining foals were randomly allocated to a feed treatment, and their owners were provided with an initial supply of the diet for that treatment and asked to gradually change their foals onto this diet over the subsequent week.

In total, 13 crib-biting foals and 8 control foals (belonging to 13 different owners) were recruited. Comparisons were made between the two populations and are summarised in Table 1.

Table 1 General Characteristics of Study Population

	Crib-biting foals		Normal foals	
	mean	se	mean	se
Age at entry (days)+	233.7	9.21	291.2	47.45
Age at weaning (days)	172.38	9.00	183.62	15.20
Age when concentrate introduced (days)	40.0	18.1	51.2	29.80
Amount of concentrate fed prior to entry (kg)	2.64	0.30	2.61	0.40

+ Entry into the study was taken as the first date on which detailed behaviour observations were taken

Crib-biting foals had developed crib-biting behaviour at an average of 152.5 (se 20.3) days of age, or 21.8 weeks. A proportion of the foals had developed oral stereotypy prior to weaning. They had been performing stereotypic behaviour for a mean 88.7 (se 13.3) days, or 12.7 weeks, prior to entry into the study.

Treatments

Six crib-biting and four control foals were allocated to a typical base diet containing cereals (wheat, barley, oats), wheatfeed, soya bean meal, peas, full fat linseed, vitamin and mineral supplements, and molasses. This base diet was supplemented with forage (fresh or preserved). This is Diet A. This diet was re-bagged before delivery to the owners and was fed according to body weight.

Seven crib-biting and three control foals were allocated to an antacid diet. This was Diet A, re-bagged and supplied with a tub of Neigh-Lox. Owners were asked to feed

approximately 125g of Neigh-Lox per day, divided equally among feeds.

One control foal for which initial samples and endoscopy results were obtained was not placed on a diet as its crib-biting partner moved to a different yard.

Behavioural Observations

Participants were visited regularly throughout the trial. Owners were asked to ensure that their foal was in an environment where it had been observed crib-biting for at least one hour before the behaviour recordings were started. The time of day, and time in relation to meal-time, that observations were taken varied among foals, but was generally held constant for each foal in the study across repeated visits.

Endoscopy

Foals were endoscoped during the first week of the trial, and a week after the trial had ended. All foals were deprived of all feed and forage for a period of 12 hours overnight and endoscoped between 0900 and 1030 hours the next morning. During endoscopy. A continuous video record was made of the glandular and squamous mucosa. Samples of gastric fluid were taken and the pH measured. The veterinarian performing the endoscopy then provided a written description of his observations. An independent observer who was not given information about which horses were crib-biters, or about which feed treatment they had received also prepared a descriptive account from the video recordings. This was compared and the written description prepared at the time by the veterinarian. The information was summarised according to an agreed scoring system.

RESULTS

Baseline correlations among variables and differences between crib-biting and normal foals at the start of the trial.

(i) General Characteristics

None of the normal foals started to crib-bite during the trial.

There were no significant differences between crib-biting and normal foals in any of the general population parameters, although despite very small numbers, there was a trend towards an association between crib-biting and previous administration of antibiotics.

(ii) Endoscopy

Endoscopy records were obtained for 10 crib-biting and 4 control horses at the start of the trial.

Ulcers were observed in 6 foals at the start of the trial. The ulcers were few in number and generally mild, with the exception of 1 crib-biting foal that had extensive ulceration. The crib-biting foals had higher scores for number of bots, severity of ulcers and inflammation than the normal foals at the start of the trial, and lower scores for stickiness of the mucosa, black flecks on the mucosa, corrugations of the squamous mucosa and folding of the glandular mucosa. The squamous mucosa and glandular mucosa were also less moist in crib-biting than normal foals.

The mean pH of the gastric fluid samples taken from 5 crib-biting foals on the first endoscopy visit was 1.69 with a range between 1.43 and 2.00.

Treatment Effects

(i) Behaviour

The data on frequency and duration of crib-biting is shown in Tables 2 and 3. It should be noted that the management of some of the foals changed during the course of the study. These foals were No. 1: in all the time (observations 1 and 2) to out all the time (observation 3); No. 3: in at night or in all of the time if wet (observations 1 and 2) to out all of the time (observation 3); and No. 13: hay fed as forage (observations 1 and 2) to haylage fed as forage (observation 3). The third observation period for these 3 foals was therefore not used in analysis.

Table 2 The frequency of crib-biting (mean bites per hour) exhibited during the trial

Foal	Diet	Obs period 1	Obs period 2	Obs period 3
1	Control	187.3	85.5	(3.8)
2	Control	5.5	0.0	0.0
3	Control	220.0	449.0	(225.0)
4	Control	48.4	2.5	0
5	Control	11.5	0.5	3.25
6	Control	62.7	70.0	73.5
7	Neighlox	4.5	0.5	0.0
8	Neighlox	60.5	478.5	155
9	Neighlox	285.3	204.9	223
10	Neighlox	111.5	47.7	Deceased
11	Neighlox	30.0	16.3	9.00
12	Neighlox	13.5	20.5	13.9
13	Neighlox	41.25	16.75	(100)

Table 3 - The duration of crib-biting (mean seconds per hour) exhibited during trial

Foal	Diet	Obs period 1	Obs period 2	Obs period 3
1	Control	894.5	821.5	(22)
2	Control	41.5	0.0	0.0
3	Control	976.0	2326.0	(691.0)
4	Control	278	23.3	0
5	Control	148	8.3	18.0
6	Control	599.7	574.5	674
7	Neighlox	89.2	5.0	0.0
8	Neighlox	364.8	2328.5	1007.0
9	Neighlox	1767.0	945	1278
10	Neighlox	455.5	172.2	Deceased

The change in crib-biting frequency and duration was assessed by taking the slope of the values over the 3 month period. Four of the 13 crib-biting foals had positive slope values for both frequency and duration, indicating an overall increase in crib-biting behaviour during the trial. The remaining slopes were all negative.

Each foal was then ranked according to its change in behaviour over time, relative to the other foals in the study. The two measures of frequency and duration resulted in slightly different rank orderings of the foals. For both measures rank order 1 indicates the foal that showed the largest decline in crib-biting, and rank order 13 indicates the foal that showed the largest increase in crib-biting. The rankings are shown in Table 4 and were used to examine associations between stomach condition and behavioural change.

Table 4 Rank ordering of foals according to change in crib-biting behaviour during trial

Foal	Rank Order for frequency	Rank order for duration
1	1	5
2	8	9
3	13	13
4	5	3
5	7	6
6	11	11
7	9	7
8	12	12
9	3	2
10	2	1
11	6	4

Foal	Rank Order for frequency	Rank order for duration
12	10	10
13	4	8

(ii) Endoscopy

Valid endoscopy records were obtained for 8 crib-biters and 3 normal horses. Positive correlations were obtained between the presence of ulcers and the presence of bots, between the presence of bots and inflammation of the mucosal surface, and between the presence of ulcers and inflammation of the mucosal surface.

The crib-biting foals had higher scores for number of bots, number of ulcers, and inflammation than the normal foals, and lower scores for stickiness of the mucosa, corrugations of the squamous mucosa and foling of the glandular mucosa, results that were very similar to the starting conditions. However, in contrast to the start of the trial the squamous mucosa and glandular mucosa were moister in crib-biting than normal foals.

Data from crib-biting and normal horses were combined and subjected to analysis to examine the effects of dietary treatment on stomach condition. At the end of the trial, horses that had received Neigh-Lox had fewer ulcers and less inflammation than horses that had received the control diets. Eight horses had noticeable ulcers at the start of the trial. Those with mild ulcers that were fed Neighlox all resolved by the end of the trial. Those with moderate or severe ulcers that were fed Neigh-Lox either showed no improvement or got worse. The ulcers of horses that were fed the control diet showed no change or got worse; none of these ulcers resolved spontaneously.

The relationship between ulcers and crib-biting behaviour was examined by comparing the extent to which crib-biting changed over the course of the trial, with the severity of ulcers present at the end of the trial. Horses whose ulcers did not heal during the course of the trial were also the horses that showed little or no reduction in crib-biting behaviour.

The results presented here demonstrate for the first time a relationship between stomach condition and abnormal oral behaviour in the horse and are consistent with crib-biting being an adaptive attempt to reduce stomach acidity. Crib-biting foals tended to have more bots and ulcers, a drier and more expanded stomach wall, and a greater degree of inflammation than normal foals. The general appearance of the stomach of the crib-biting foals supports the hypothesis that their stomachs are more acid. The results also show that an improvement in stomach condition was associated with reduced crib-biting behaviour. Administration of Neigh-Lox was associated with a resolution of mild ulceration. Foals whose mild ulceration cleared showed the greatest improvement in crib-biting. In some of these foals crib-biting ceased altogether.

The cause of the stomach problems in crib-biting foals is not clear. Candidate factors include:

- The early introduction of concentrate feed.

Most of the crib-biting foals in the study had received concentrate feed from birth, or during the pre-weaning period. It is known from other work that concentrate feed increases gastric acidity, and causes ulceration.

- Previous illness or use of antibiotics.

The owners of some foals reported that they had started crib-biting during a period of illness or after receiving antibiotics. Illness may involve confinement and separation and foals may not feed properly during such periods.

Alternatively, antibiotics may have a more direct effect in disrupting the flora of the hindgut.

- Sustained effects originating at weaning.

Weaning by methods that are particularly stressful increases the rate of development of steriotypies dramatically. Stressed foals are unlikely to eat, and feed deprivation is known to increase gastric acidity.

- Differential production of saliva.

It is possible that there is variation among foals in the extent to which they release saliva, either spontaneously or during feeding. The production of a limited supply of saliva may cause or enhance stomach acidity. The foals that do the most crib-biting may be the ones that most need to produce saliva and are most frustrated by their inability to do so in sufficient quantities.

The data presented in the example demonstrate the effectiveness of a stomach antacid on the prevention, treatment, or amelioration of *equine* crib-biting. This activity is thought to be enhanced by the inclusion in compositions according to the invention of fat and fibre.

Compositions and methods according to the invention may be particularly effective at preventing stereotypy when the animal being treated is a weaning or recently weaned animal. Foals are typically weaned when they are four to six months old.

Use of compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of any stereotypy in all *equidae*, non-ruminant herbivores, and non-ruminant omnivores, for example crib-biting, wind-sucking, weaving and box-walking in equine animals.

Use of compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of stereotypies linked with gut function in all *equidae*, non-ruminant herbivores, and non-

ruminant omnivores, but especially in the amelioration, treatment or prevention of equine crib-biting.

The reason that compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of animal stereotypy is not known. However, the realisation that low stomach pH is linked with stereotypic behaviour suggests that pain caused by low stomach pH may cause the animal to perform a stereotypy, such as crib-biting, to stimulate the flow of saliva into the stomach. This saliva would be expected to increase the stomach pH and alleviate the pain. The fact that significant numbers of horses develop stereotypic behaviour during the immediate post-weaning period may be because the diet of a foal changes significantly during weaning. If such a dietary change results in a persistent decrease in stomach pH, then stereotypic behaviour may be more likely to occur. Administration of compositions according to the invention to an animal, especially a weaning or recently weaned animal, may ensure that its stomach pH is not persistently low and remove, therefore, the need for the animal to stimulate the flow of saliva into the stomach. It is believed that the fibre may help to prolong the time spent chewing by an animal. This in turn prolongs the production of saliva which neutralises stomach acid. The fat is thought to delay emptying of the stomach so that the beneficial effect of the antacid and/or fibre is prolonged.

Compositions according to the invention may act by preventing or reducing stomach ulcer formation caused by prolonged periods of low stomach pH, or by treating stomach ulcers already formed.

Compositions and methods according to the invention may be significantly more effective in the treatment and prevention of animal stereotypy than prior treatments and preventatives. In addition, treatment of animals using compositions and methods according to the invention does not

involve any undesirable practices being performed on the animal.

Claims

1. A composition for use in the treatment, prevention or amelioration of animal stereotypy which comprises fat, fibre, and optionally a stomach antacid.

2. A pharmaceutical composition for use in the treatment, prevention or amelioration of animal stereotypy which comprises fat, fibre, and optionally a stomach antacid, together with a pharmaceutically acceptable carrier, excipient or diluent.

3. A composition according to claim 1 or 2 in which the amount of fat in the composition is from about 5% to about 20%, preferably from about 8% to about 17%, by weight of the composition.

4. A composition according to any preceding claim in which the amount of crude fibre in the composition is from about 3.5% to about 35%, preferably from about 10% to about 25%, by weight of the composition.

5. A composition according to any preceding claim in which the amount of neutral detergent fibre in the composition is from about 15% to about 70%, preferably from about 25% to about 50%, by weight of the composition.

6. A composition according to any preceding claim in which at least some of the fibre is chopped fibre.

7. A composition according to claim 6 in which at least some of the chopped fibre is about 1-7cm long.

8. A composition according to any preceding claim in which the starch content of the composition is low, preferably below about 20% by weight of the composition.

9. A composition according to any preceding claim in which the antacid inhibits secretion of acid in the stomach.

10. A composition according to claim 9 in which the antacid is a proton pump inhibitor such as omeprazole, or a histamine type-2 antagonist.

11. A method of treatment, prevention or amelioration of animal stereotypy which comprises controlling the stomach pH of an animal.

12. A method according to claim 11 in which the stomach pH of the animal is controlled before any stereotypic behaviour performed by the animal becomes fixed.

13. A method according to claim 11 in which the stomach pH of the animal is controlled before, or shortly after, it develops any stereotypic behaviour.

14. A method according to claim 11, 12 or 13 in which the animal is a weaning, or recently weaned animal.

15. A method according to claim 11, 12 or 13 in which the animal is a weaned animal.

16. A method according to any of claims 11 to 14 in which the stomach pH of the animal is controlled from birth.

17. A method according to any of claims 11 to 16 in which the stomach pH of the animal is controlled by inhibiting secretion of acid in the stomach of the animal.

18. A method according to claim 17 in which the acid secretion is inhibited by administering a proton pump inhibitor, such as omeprazole, or a histamine type-2 antagonist to the animal.

19. A method according to any of claims 11 to 18 in which the stomach pH of the animal is controlled by administering a composition according to any of claims 1 to 10 to the animal.

20. A method according to claim 19 in which the composition is included in the animal's diet from birth.

21. A method according to claim 19 or 20 in which the composition is included in the diet of the animal's mother when she is lactating.

22. A method according to any of claims 19 to 21 in which the composition is included in feed and the said feed is fed to the animal as it is being weaned.

23. A method according to any of claims 11 to 22 in which the stomach pH of the animal is controlled shortly before and/or during and/or following weaning, ingestion of a high grain diet, or a period of extended fasting by the animal.

24. A method of treatment, prevention or amelioration of animal stereotypy which comprises preventing or reducing ulcer formation, or treating ulcers formed in the stomach of an animal.

25. A method according to claim 24 in which ulcer formation is prevented or reduced, or ulcers are treated, by administering a composition according to any of claims 1 to 10 to the animal.

26. Use of a composition comprising a stomach antacid in the manufacture of a medicament for the amelioration, treatment, or prevention of animal stereotypy.

27. Use of a composition according to any of claims 1 to 10 in the manufacture of a medicament for the amelioration, treatment or prevention of animal stereotypy.

28. A method according to any of claims 11 to 25 or use according to claim 26 or 27 in which the animal is an *equidae*, a non-ruminant omnivore, or a non-ruminant herbivore.

29. A method or use according to claim 28 in which the animal is a horse.

30. A method or use according to claim 29 in which the stereotypy is crib-biting.

31. A composition substantially as described.

32. A pharmaceutical composition substantially as described.

33. A method substantially as described.

2296.2320

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT COOPERATION TREATY APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled ANIMAL STEREOTYPY

the specification of which was filed as PCT International Application No. PCT/GB99/03288 on October 6, 1999 and was amended under PCT Article 19 on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) on which priority is claimed:

Country	Application No.	Filed (Day/Mo./Yr.)	Priority Claimed (Yes/No)
U.K.	9821790.4	6 October 1999	YES
U.K.	9822563.4	15 October 1998	YES

I hereby appoint the practitioners associated with the firm and Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to the address associated with that Customer Number:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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